

BRIEF REPORT

Multi-centre study concluded that the severe acute respiratory syndrome coronavirus 2 was not a primary cause of bronchiolitis in infants

Bronchiolitis is one of the most common viral infections in infants and the respiratory syncytial virus has been the most frequently associated pathogen with this disease.¹ The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which causes COVID-19, typically presents with respiratory symptoms.² Although SARS-CoV-2 has been reported to be a possible rare cause of bronchiolitis,² further research is needed to understand this relationship. The aim of this study was to explore the hypothesis that SARS-CoV-2 was one of the respiratory viruses that caused bronchiolitis in Italy.

This multi-centre case-control study included all infants up to 1 year of age that fulfilled the inclusion criteria between 1 October 2021 and 31 March 2023 when they presented to the paediatric departments of three Italian hospitals. These were the Ca' Granda Ospedale Maggiore in Milan, the Gemelli Hospital in Rome, and the Institute for Maternal and Child Health Burlo Garofolo in Trieste. A comprehensive and systematic approach was implemented to investigate the potential presence of the SARS-CoV-2 virus in paediatric

patients in these hospitals during the study period. All patients accessing the emergency departments with respiratory symptoms underwent a nasopharyngeal swab to detect SARS-CoV-2. In addition, all paediatric patients requiring short-stay observations or hospitalisation after presenting to the emergency department underwent a nasopharyngeal swab for SARS-CoV-2, regardless of their clinical signs or symptoms.^{3,4}

Patients were diagnosed with bronchiolitis if they had experienced an acute upper respiratory tract infection in the week leading up to their emergency department visit, followed by the sudden onset of respiratory distress. The diagnosis also included a cough and widespread crackling sounds during lung auscultation. Infants with a diagnosis of bronchiolitis were included as cases. The controls were infants who required hospitalisation for other reasons, such as head traumas or accidental poisoning, without any infectious symptoms or signs consistent with a SARS-CoV-2 infection, as previously described.^{3,4} The controls were also tested for SARS-CoV-2. We retrospectively collected information on the children's age and

TABLE 1 Characteristics of the sample and comparison between infants with bronchiolitis (cases) and infants without any signs or symptoms consistent with a SARS-CoV-2 infection (controls).

Unadjusted analyses ^a				
	Total sample	Cases	Controls	<i>p</i>
<i>N</i>	1624	948	676	
Median age in months [IQR]	3.2 [1.5–6.6]	3.2 [1.5–6.6]	3.4 [1.2–7.8]	0.349
Male sex	57%	55%	58%	0.335
SARS-CoV-2 positive <i>n</i> (%)	5%	3%	8%	<0.001
Adjusted analysis – multiple logistic regression model ^b				
	Odds ratio	Lower 95% CI	Upper 95% CI	<i>p</i>
Age (months)	1.01	0.94	1.07	0.858
Sex (male)	0.72	0.46	1.13	0.159
Population (cases)	0.42	0.27	0.67	<0.001

Abbreviation: CI, confidence interval.

^aVariables compared with two-tailed Fisher's exact test and the Mann–Whitney *U* test.

^bMultiple adjusted regression model. Testing positive was a dependent variable.

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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sex, other respiratory viruses affecting the cases and the reason why controls were admitted.

Our aim was to assess whether infants with bronchiolitis (cases) tested positive for SARS-CoV-2 more frequently than infants without any signs or symptoms consistent with a SARS-CoV-2 infection (controls). We evaluated the frequency of positive tests in the two groups using a two-tailed Fisher's exact test. The Mann-Whitney *U* test was used to compare the continuous variables. In addition, logistic regression models were performed. The SARS-CoV-2 results were the dependent variables, being a control or a case was the predictive variable and the data were adjusted for age and sex. A *p* value of <0.05 was considered significant. R version 3.5.3 (The R Foundation, Vienna, Austria) was used for the statistical analyses.

We enrolled 1624 infants: 948 (58%) cases and 676 (42%) controls. The characteristics of the study population are provided in Table 1. The SARS-CoV-2 infection was detected in 5% of the total sample. Any virus was detected in 526 cases and the respiratory syncytial virus was the most frequent (62%). We found that 21 cases concurrently tested positive for SARS-CoV-2 and the respiratory syncytial virus. The most frequent reasons for hospitalising the controls were suspected surgical (42%) or neurological (27%) diseases.

Cases tested positive for SARS-CoV-2 less frequently than controls (3% vs. 8%, respectively, *p* < 0.001). The regression model (Table 1) indicated that having bronchiolitis was inversely associated with testing positive for SARS-CoV-2 (odds ratio 0.42, 95% confidence interval 0.27–0.67). When cases of co-infection by SARS-CoV-2 and the respiratory syncytial virus were excluded, the association became even stronger (odds ratio 0.14, 95% confidence interval 0.07–0.27).

The frequency of SARS-CoV-2 asymptomatic carriers was less than 10% in this study, which was consistent with previous data.³ More interestingly, infants with bronchiolitis tested positive for SARS-CoV-2 less frequently than the other infants. On the one hand, this unexpected result might be explained by the viral competition among different types of viruses in infecting host cells.⁵ On the other hand, this finding does not support the hypothesis that SARS-CoV-2 can account for bronchiolitis. These findings may have important implications for overcrowded emergency departments, social isolation rules or testing policies. It suggests that these should not negatively affect patients' care, as the risk that children with bronchiolitis were SARS-CoV-2 positive was very low in our study.

Some limitations should be considered. Despite the potential relevance of this study, it was retrospective and it was a hospital-based investigation that only involved three centres. On the other hand, these hospitals followed well-defined, standardised procedures for testing SARS-CoV-2 infections during the study period.

In conclusion, bronchiolitis remains a prevalent viral infection among infants, with the respiratory syncytial virus being the predominant pathogen. While SARS-CoV-2 has been shown to present with respiratory symptoms, this study suggests that this virus cannot be considered a primary cause of bronchiolitis in infants. Further studies are necessary to investigate the relationship between the SARS-CoV-2 infection and its respiratory manifestation in infants.

AUTHOR CONTRIBUTIONS

Danilo Buonsenso: Conceptualization; investigation; writing – original draft; writing – review and editing; methodology; data curation.

Gregorio P. Milani: Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; project administration; data curation; formal analysis.

Paola Marchisio: Conceptualization; supervision; writing – review and editing. **Carlo Agostoni:** Conceptualization; writing – review and editing; supervision.

Ilaria Alberti: Methodology; data curation; writing – review and editing. **Rosa Morello:** Data curation; investigation; writing – review and editing. **Alessandro Zago:** Writing – review and editing; data curation; investigation. **Giorgio Cozzi:** Investigation; writing – original draft; writing – review and editing; methodology; data curation.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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